Title

A Multicenter Randomized Placebo-Controlled Trial of Intravenous Thyroxine for Heart-Eligible Brain Dead Organ Donors

Protocol ID: **ODRC-002**

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Study Principal Investigator:

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Abstract

Background: Brain death frequently induces hemodynamic instability and cardiac stunning. Impairments in cardiac performance are major contributors to hearts from otherwise eligible organ donors not being transplanted. Deficiencies in pituitary hormones (including thyroid-stimulating hormone) may contribute to hemodynamic instability and replacement of thyroid hormone has been proposed as a means of improving stability and increasing hearts available for transplantation. Intravenous thyroxine is commonly used in donor management. However, small controlled trials have not been able to demonstrate efficacy.

Methods: This multicenter study will involve organ procurement organizations (OPOs) across the country. A total of 800 heart-eligible brain dead organ donors who require vasopressor support will be randomly assigned to intravenous thyroxine for at least 12-hours or saline placebo. The primary study hypotheses are that thyroxine treatment will result in a higher proportion of hearts transplanted and that these hearts will have non-inferior function to hearts not treated with thyroxine. Additional outcome measures are time to achieve hemodynamic stability (weaning off vasopressors) and improvement in cardiac ejection fraction on echocardiography.

Discussion: This will be the largest randomized controlled study to evaluate the efficacy of thyroid hormone treatment for organ donor management. By collaborating across multiple OPOs, it will be able to enroll an adequate number of donors and be powered to definitively answer the critical question of whether intravenous thyroxine treatment increases hearts transplanted and/or provides other hemodynamic benefits.

Trial registration: registered at clinicaltrials.gov under **NCT04415658**

Keywords

Brain death; Organ donation; Heart transplant; Thyroid hormone; Donor management

Protocol Summary

Title:	A Multicenter Randomized Placebo-Controlled Trial of Intravenous Thyroxine for Heart-Eligible Brain Dead Organ Donors
Precis:	This randomized non-blinded study will compare intravenous thyroxine (T4) to saline placebo in 800 brain dead organ donors who have provided authorization for research and are eligible for heart transplantation based on age and lack of exclusions
Objectives	Primary: Intravenous thyroxine (T4) will increase the proportion of hearts transplanted when given early after brain death to heart-eligible hemodynamically unstable potential organ donors Safety: Hearts transplanted from donors receiving T4 will have non-inferior 30-day graft survival to those from the placebo group Secondary: T4 will reduce time to wean off vasopressors and improve cardiac ejection fraction
Endpoints	The primary outcome is the proportion of hearts transplanted (the number of hearts transplanted divided by the total number of potential donors). The safety outcome is proportion of hearts transplanted that maintain graft function at 30-days and 1-year. Secondary outcomes will include: 1) time from randomization to weaning off vasopressors: defined as being off all vasoactive agents (except for vasopressin); 2) proportion weaned off vasopressors by 12-hours (same criteria as #1); 3) time achieving hemodynamic stability adequate to order first echocardiograph; 4) left ventricular ejection fraction measured on first donor echocardiography; 5) total number of organs transplanted
Population	We plan on enrolling 800 brain dead organ donors with authorization for donation and research in order to have 752 evaluable subjects who receive the study drug or placebo
Phase	Three
Number of Sites	Est. 10 OPOs, 1 coordinating site for human (recipient) data
Study Duration	18-24 months

Abbreviations

AOPO, Association of Organ Procurement Organizations

BD, brain dead

DSMC, data and safety monitoring committee

LVEF, left ventricular ejection fraction

OPO, organ procurement organization

ODRC, Organ Donation Research Council

OPTN, Organ Procurement and Transplant Network

SRTR, Scientific Registry of Transplant Recipients

T4, thyroxine

TTE, transthoracic echocardiography

UNOS, United Network for Organ Sharing

Administrative information

Title {1}	A Multicenter Randomized Placebo-Controlled Trial of Intravenous Thyroxine for Heart-Eligible Brain Dead Organ Donors
Trial registration {2a and 2b}.	Clinicaltrials.gov NCT04415658. Registered June 4, 2020. https://clinicaltrials.gov/ct2/show/NCT04415658
Protocol version {3}	2.0
Funding {4}	None (internal administrative support provided by Mid-America Transplant)
Author details {5a}	Rajat Dhar, Washington University in St. Louis School of Medicine Gary Marklin, Mid-America Transplant
Name and contact information for the trial sponsor {5b}	Mid-America Transplant 1110 Highlands Plaza Drive, #100 Saint Louis, MO 63110
Role of sponsor {5c}	Mid-America Transplant will not have any role in the design or analysis of the trial data. They will not have any role in the writing of the manuscript or the decision to submit the report for publication.

Introduction

Background and rationale {6a}

Brain death frequently induces hemodynamic instability and cardiac stunning (1, 2). Impairments in cardiac performance are major contributors to hearts from otherwise eligible organ donors not being transplanted (3). Deficiencies in pituitary hormones (including thyroid-stimulating hormone) may contribute to hemodynamic instability (4, 5). Replacement of thyroid hormone has been proposed as a means of improving stability and increasing hearts available for transplantation (6). Intravenous thyroxine is now commonly used in donor management across the United States, either for all donors or only those with hemodynamic instability or those who are being considered for heart donation (7, 8). Large retrospective studies have found associations between use of hormonal resuscitation, including thyroid hormone, and more hearts transplanted (7, 9). However, several small controlled trials have not been able to confirm efficacy of thyroid hormone in improving heart function after brain death or increasing the chances of hearts being transplanted (10, 11).

We recently performed two small parallel single-center randomized studies of thyroid hormone in heart-eligible brain dead (BD) organ donors. The first evaluated whether intravenous triiodothyronine (T3) was superior to thyroxine (T4) in hemodynamically unstable BD donors with cardiac stunning (12). This was based on the rationale (supported by some experimental data) that T3 is the active hormone and its levels decline more rapidly after brain death (13). We were able to measure cardiac performance (left ventricular ejection fraction, LVEF) both immediately prior to starting infusion of T3 or T4 and immediately after eight hours of therapy. This physiologic proof-of-principle study demonstrated that LVEF improved comparably in both groups over this short time frame (from 38-45% to 50-53%) and both groups could be progressively weaned off vasoactive agents prior to organ recovery. Furthermore, after adjusting for group imbalances (likely due to small study size), hearts were transplanted in a similar proportion of the T3 and T4 groups (rate of heart utilization was 43% in this population). This study did not support the superiority of T3 (a more expensive intervention) over T4 in the management of unstable BD heart donors.

Our next study aimed to test whether T4 infusion would be superior to placebo in heart-eligible donors with reduced LVEF despite being off vasopressors. Both studies aimed to enroll and start infusion within 12 hours of BD (at least defined by time when declaration occurred). Neither studies were blinded but evaluation of LVEF was performed blind to treatment allocation. Median improvement in LVEF was 10% with T4 compared with 5% without thyroid hormone (p=0.24), although intention-to-treat efficacy analysis was limited by the fact that several of those randomized to T4 either did not receive or had this intervention discontinued prematurely due to emergent hypertension or tachycardia (14). There was a trend to more hearts being transplanted in the T4 group (59 vs. 27%, p=0.14) as well as more organs in total transplanted per donor (median of 5 vs. 3, p=0.009). Although this study suggested that thyroid hormone could be efficacious in increasing hearts transplanted, definitive conclusions were precluded by its small sample size (a consequence of enrolling at only one OPO) and group imbalances despite randomization. Therefore, we believe that there remains scientific equipoise and significant interest amongst the OPO and transplant communities in determining whether thyroid hormone does actually improve heart function and result in more

hearts transplanted.

In fact, scientific research to determine the optimal interventions for donor management have been receiving increasing interest (15). To date, most studies have been retrospective and not adequately controlled (16, 17). Recently, OPOs have begun collaborating more intently to answer important donor management questions. A council focused on research was formed as part of the *Association of Organ Procurement Organizations* (AOPO). This Organ Donation Research Council (ODRC) aims to bring together OPOs and interested parties (such as transplant physicians and scientists) to advance the science of organ and tissue donation. Collaborations nurtured as part of ODRC led to a multi-center randomized study that demonstrated that naloxone, frequently used (based on retrospective studies) to improve lung function, did not actually improve oxygenation or result in more lungs transplanted than a saline placebo (18). A few other randomized donor management studies have been performed (19-21).

Objectives {7}

Primary: Intravenous thyroxine (T4) will increase the proportion of hearts transplanted when given early after brain death to heart-eligible hemodynamically unstable potential organ donors

Safety: Hearts transplanted from donors receiving T4 will have non-inferior graft survival to those from the placebo group at 30-days

Secondary: T4 will reduce time to wean off vasopressors and improve cardiac ejection fraction

Trial design {8}

Randomized in parallel groups to intravenous thyroxine or saline placebo in 1:1 ratio
Randomization will be in blocks, stratified by OPO site, allowing each site to serve as its own control (given heterogeneity in donor management protocols between OPOs)
Administration of study drug or placebo will not be blinded

Methods: Participants, interventions and outcomes

Study setting {9}

This study will be performed under the auspices of various Organ Procurement Organizations (OPOs) across the country (full list will be available on clinicaltrials.gov). Participants will be patients already declared dead by neurologic criteria (i.e. brain dead) and who have provided authorization (first-person or by living surrogates) for both organ donation and for research. They may be physically located either/both in the hospitals in which they were declared and/or at an independent recovery/donor management facility of the OPO. The donor component has been deemed not to involve human subjects research and participating hospitals and OPOs are therefore not engaged in human subjects' research. The coordinating site (Washington University in St. Louis) will be the research site responsible for collecting recipient outcome data. A waiver of consent has been obtained for this human recipient data.

Eligibility criteria {10}

Inclusion Criteria:

1. Declared dead by neurologic criteria
2. Provided authorization for organ donation and for research
3. Donor age of 14-55 years (inclusive) and weight ≥ 45 kg (100 lbs)
4. On one or more vasopressor and/or inotropes (not including vasopressin)

Exclusion Criteria:

1. Brain death declared > 24 hours prior
2. Known CAD or MI (by history, EKG, or previous cardiac cath)*
3. Significant valvular heart disease (by history of echo)*
4. Prior sternotomy or cardiac surgery*
5. Donor at VA hospital
6. Received intravenous or oral thyroid hormone in the past month
7. Known HIV+ status
8. Other reason preventing donor from receiving study drug (determined by on-site coordinator)

   * sufficient to exclude donor heart from being considered for transplantation

Who will take informed consent? {26a}

Donors are dead and their surrogates have provided authorization for research. This is verified by organ procurement coordinators who are managing the donor management process. Recipients of organs from those enrolled in this study are human subjects but we have obtained a waiver of consent to collect de-identified graft function/outcome data on those receiving hearts from donors enrolled in this trial.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

All data utilized for analysis will be collected as part of donor care including standard UNOS and SRTR data variables (e.g. demographics). No additional biologic specimens will be collected.

Interventions

Explanation for the choice of comparators {6b}

Intravenous thyroxine (T4) is commonly employed at almost all OPOs around the country as part of standard hormonal resuscitation, either for all donors or only those who are hemodynamically unstable (8). It is recommended (without level I evidence) in several donor management guidelines (22). It is usually given as an infusion with or without an initial bolus (protocols vary). A pilot randomized comparison of thyroid hormone formulations (T3 vs. T4) did not suggest any important benefits of T3 over T4 (12). Treatment with T4 will be compared to no thyroid hormone (during the first twelve hours, open-label T4 may be used after).

Intervention description {11a}

Study infusion (saline or thyroxine) will be commenced as soon as possible after randomization. Serum free T4 and TSH levels will be drawn prior to giving the drug. The T4 will be prepared by mixing 500 µg of drug in

500-ml of normal saline (i.e. concentration of 1 µg/ml) and enclosing the bag in an opaque sleeve. The placebo will be a 500-ml bag of normal saline (without active drug) also enclosed in an opaque sleeve. The infusion from this bag will be started at 30 ml/hour (corresponding to 30 µg/hour) and run for at least 12 hours, unless adverse effects occur and the infusion is stopped prematurely (see titration protocol below). Vasoactive medications will be weaned as expeditiously as possible. When the donor is considered hemodynamically stable, initial transthoracic echocardiography (TTE) will be ordered and obtained as soon as possible. Repeat serum free T4 level should be drawn prior to organ recovery in both groups. Organ allocation will proceed per OPTN policy and routine allocation practices. All other aspects of donor management will also follow local OPO protocols.

Criteria for discontinuing or modifying allocated interventions {11b}

Titration protocol: T4 can be titrated down if:

a) Systolic Blood Pressure above 180 mm Hg and increase of 30 mm Hg above baseline
b) Heart rate over 120 bpm and increase by 20 bpm above baseline
c) New tachyarrhythmia (atrial fibrillation, atrial flutter, superventricular tachycardia, ventricular tachycardia) or new onset ectopy (ventricular premature contractions > 6/min)
d) Other significant change, at discretion of the coordinator

The dose should be reduced in increments of 10 µg/hour (i.e. to 20 then 10µg/hour). The infusion can be discontinued if hemodynamic instability persists despite weaning.

Open-label T4 can be given to the placebo group after 12-hours at the discretion of the managing team (whether for persistent hemodynamic instability, low EF on echo, or physician preference). T4 can also be continued beyond 12-hours of study infusion for the same reasons in the intervention group.

Strategies to improve adherence to interventions {11c}

There will be a one-month run-in period at each site where screening logs will be checked by the site and central study coordinators for completeness and accuracy. They will review all cases where donors were not enrolled within 24 hours or if other reasons for ineligibility were provided and provide feedback. The site and study coordinators will have weekly conference calls for the first month (and then monthly thereafter) to discuss issues with adherence. They will also provide feedback to individual OPO personnel if study protocols are violated. The study statistician will perform monthly audits of study data for completeness.

Relevant concomitant care permitted or prohibited during the trial {11d}

All standard OPO donor management practices will be continued throughout the study period until and including organ allocation and recovery. The only intervention prohibited is administration of thyroid hormone to those donors allocated to the placebo group for the first 12 hours after randomization.

Provisions for post-trial care {30}

Data collection on non-human organ donors ends at time of organ procurement or end of donor management (for authorized brain-dead potential donors who do not go on to donate organs).

Outcomes {12}

The primary outcome for this study is the proportion of hearts transplanted (the number of hearts transplanted divided by the total number of potential donors – including those authorized but not recovered).
The primary safety outcome for this study is 30-day graft survival in those receiving hearts from those enrolled in this study. This is defined by patient survival with the originally transplanted heart and no mechanical circulatory support. It will be assessed primarily at 30-days but also at 1-year.
Secondary outcomes will include:

1. Time from randomization to weaning off vasopressors: defined as being off all vasoactive agents, except for vasopressin (≤ 1 U/hr)
2. Proportion weaned off vasopressors by 12-hours (same criteria as #1)
3. Vasopressor-inotrope score at 12-hours (excluding vasopressin ≤ 1 unit/hour)
4. Time achieving hemodynamic stability adequate to order first echocardiography
5. Ejection fraction measured on first donor echocardiography
6. Lungs and total thoracic organs transplanted
7. Total number of organs transplanted
8. Additional outcomes routinely collected from heart transplant recipients will also be aggregated and analyzed, including need for post-transplant mechanical circulatory support and other measures of primary graft dysfunction

Safety endpoints:
The following adverse events will be prospectively collected on all study donors. All events deemed either related or potentially related to the study drug infusion will be reviewed by the site coordinator. Any serious related events (defined as hemodynamic instability leading to cardiac arrest or donor loss prior to organ recovery) will be forwarded to the DSMC for additional review:

1. Severe hypertension (systolic BP > 200 mm Hg)
2. Tachycardia (HR > 150 and increased more than 20 over baseline)
3. New/worsened tachyarrhythmia (SVT, Atrial fibrillation, Ventricular tachycardia or fibrillation)
4. Cardiac arrest or any donor loss prior to the OR
5. Fever – new, above 102 degrees Celsius
6. New skin rash

Participant timeline {13}

	STUDY PERIOD								Heart Recipient	
	Screening	Allocation	Infusion Period					Organ Recovery		
TIMEPOINT		t0	*2*	*4*	*6.*	*..*	*12*	*Time OR*	*30-days*	*1-year*
ENROLMENT:										
Eligibility screen	X									
Confirm research authorization	X									
Randomization		X								
INTERVENTIONS:										
Thyroid hormone or saline infusion		←					→			
ASSESSMENTS:										
Vital signs and vasopressor doses	X	X	X	X	X	X	X	X		
Free T4 level		X						X		
TTE				X		X				
Heart / Organs Transplanted								X		
Heart Graft Survival									X	X

Sample size {14}

In order to detect an increase in the proportion of hearts transplanted from 35% to 45%, we will need 752 total donors (376 per group), assuming 80% power and an alpha of 0.05. Because we expect some loss of donors after enrollment (e.g., clinical issues that interrupt adherence to the protocol), we will enroll a total of 800 donors (400 in each study group).

For our safety analysis in recipients of donor hearts, we have calculated a sample size necessary to demonstrate non-inferiority in graft survival with a 10% margin (see *Statistical Methods* for full explanation). Assuming 96% 30-day survival, one-sided alpha of 0.05, 90% power would require 118 donors (59 per group). Therefore, based on our sample size of donors and a conservative estimate that 35% of hearts will be transplanted, we expect 300 recipients for this analysis and should have sufficient power. Our proposed sample size would also provide 90% power to demonstrate non-inferiority at the one-year survival endpoint.

Recruitment {15}

There are between 50 and 100 heart-eligible organ donors per year managed at most OPOs (of variable sizes) around the country. Therefore we are recruiting at least 10 OPO sites (est. 50 participants per OPO per year) in order to complete recruitment of adequate donors (n=800) within a 18-month study period.

Assignment of interventions: allocation

Sequence generation {16a}

A random sequence of 1s and 0s will be computer-generated by the central coordinating site in blocks of 30 for each participating OPO site (i.e. stratified by site). A web-accessible randomization sheet will be provided to each site with three such blocks (i.e. randomization key for 90 potential subjects).

Concealment mechanism {16b}

Only once eligibility has been confirmed will the on-site organ procurement coordinator will login to the website with the randomization list and determine (using the next available row) to which group the donor has been assigned. The coordinator will enter the UNOS# of the donor on the randomization form, as well as the time and date of enrollment in the study before communicating the study assignment to OPO staff. The site study coordinator will review the randomization log to ensure that all eligible donors are being randomized and that sequential randomization rows are utilized.

Implementation {16c}

Randomization sequence of T4 vs. saline will be generated by the central coordinating statistician. Participants will be enrolled by the organ procurement coordinators at each site managing the donor after determining eligibility. They will determine the allocation to one of the study groups and assign participants to their randomized intervention.

Assignment of interventions: Blinding

Who will be blinded {17a}

Care providers will not be blinded to study groups. Organ donors (being deceased) will be unaware of treatment. Assessment of cardiac function on echocardiography will also be blinded to study group.

Procedure for unblinding if needed {17b}

The study will not be blinded to coordinators or to those performing organ allocation (e.g. transplant surgeons). Furthermore, we will ensure that it is clearly documented in DonorNet that each participant is enrolled in this study. Each participant can also receive open-label T4 at the termination of the 12-hour study period, at the discretion of the physician or study team.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Each OPO will identify a site study coordinator who will be responsible for ensuring proper completion of data collection forms. The central coordinating OPO will create the data collection forms and distribute them to each study coordinator. The central coordinating statistician will train each study coordinator on data collection and data entry procedures. *Recipient data will be collected by the central site by matching donor UNOS IDs to the SRTR database of recipient and graft outcomes. No identifiable data on recipients will be collected and this data will not be shared with the sites.*

Plans to promote participant retention and complete follow-up {18b}

No participants will be lost to follow-up as the final assessment occurs at organ recovery, which is available for all donors. However, it is possible that some donors may have incomplete data or may not finish the protocol once it is started. For example, a donor may be authorized for donation but may not become an organ donor (‘authorized, not recovered’ status). Such a donor does not undergo organ recovery and so will not have data at the final endpoint. However, we will analyze groups as randomized, i.e. by intention-to-treat, imputing these non-recovered donors as not having hearts transplanted. Similarly, we will analyze all those randomized to T4 within that study group even if they do not receive the drug or have it discontinued before 12-hours.

Data management {19}

Study-specific data will be entered onto a paper data flowsheet (Appendix A) with the UNOS ID for each participant and the assigned group marked at the top. This data sheet will be forwarded to the site study coordinator who will enter participant data into a secure REDCap database. This has built-in data validation and range checks. This study data will be supplemented by matching each enrolled donor (by UNOS ID) to their SRTR demographic data. This includes donor age, sex, and other important variables. The central coordinating statistician will perform data quality checks monthly and will work with the study coordinators at each OPO to resolve any quality issues.

Confidentiality {27}

No participant data will be shared outside of the study except when UNOS IDs are provided to the OPTN/SRTR to acquire data on whether transplanted hearts functioned and recipients survived. No recipient identifying data will be collected.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biologic specimens will be collected for this trial or for future use.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Descriptive statistics will be computed for demographic and clinical variables. If we find any differences between groups (p.<.01), those variables will be included as covariates in outcome analyses. We will also compute descriptive statistics for primary and secondary outcomes.

We expect to analyze the primary outcome, the percent of hearts transplanted, using the chi-square test. If, however, we find significant differences between groups on demographic or clinical variables that could impact heart transplant success, we will analyze our primary outcome using logistic regression with study condition as an independent variable and the relevant demographic or clinical variables as covariates. All tests will be two-tailed at a significance level of 0.05. The analysis will follow an intention-to-treat model. However, we will also perform a secondary per-protocol analysis, including only those receiving at least six hours of study infusion. We will also analyze only those in the placebo group who did not receive open-label T4, for a secondary analysis.

We will analyze the primary safety endpoint of recipient graft survival using a non-inferiority method. The null hypothesis is that heart graft survival is lower by a clinically significant margin (set at 10%) than that observed in hearts transplanted from the placebo donors. This margin was selected with input of the data and safety monitoring committee (DSMC), including a thoracic transplant surgeon and ethicist. It aligns with that used in other trials assessing graft function after heart transplantation.(23)

Our plans for analyzing the secondary outcomes are as follows. For time to get off vasopressors and time to order first echo, we will calculate Kaplan-Meier survival curves. We will calculate the vasopressor-inotrope score, VIS (24) as:

VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 100 x norepinephrine dose (μg/kg/min) + 10 x milrinone dose (μg/kg/min) + 100 x phenylephrine dose (μg/kg/min) + 10,000 x vasopressin dose (U/kg/min – only for doses > 1 U/hour)

We will compare the decrease in VIS from start of thyroid hormone or saline infusion until 12-hours (end of study infusion), using linear regression, adjusting for significant covariates (including baseline score, site).

Cardiac ejection fraction will be analyzed using the t-test if the underlying distributions are normal; if not, they will be analyzed using the Mann-Whitney U test. If we find significant differences between groups on demographics or clinical variables, we will analyze ejection fraction using linear regression with study condition as an independent variable and relevant covariates.

Thoracic and total organs transplanted will be analyzed using Poisson regression, with study group as the independent variable and expected organs transplanted as a covariate.

Interim analyses {21b}

The DSMC statistician will perform one interim analysis when 376 donors have been enrolled with evaluable data. The trial may be terminated early if, based on the judgement of the DSMC, the interim findings demonstrate either superiority or clear inferiority of T4 treatment compared to placebo (at a threshold of 0.01). The trial may also be terminated if there is inferiority of graft outcomes in either group, observed at 30-days in those hearts transplanted and observed for this period. The DSMC will provide recommendations to the study PIs, who will make final decisions about whether to stop or continue the trial.

Methods for additional analyses (e.g. subgroup analyses) {20b}

We will analyze the primary outcome (proportion of hearts donated) for each OPO individually. Sample sizes will vary between OPOs, so we may only have power to detect large effect sizes. Still, these OPO-specific analyses could provide valuable insights about trends at each OPO.

We will adjust our primary analyses for: SRTR variables determined to be important for hearts being transplanted (such as age, sex, and cause-of-death)

We will perform prespecified subgroup analyses of:

1. Time to start < 12 hours vs. > 12 hours from BD determination
2. EF result (normal, > 50%, abnormal ≤ 50%)

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Donors who are not managed according to the protocol (e.g., not managed properly on T4) will be included in the initial analyses following an intent-to-treat model. Subsequent analyses may exclude those cases in order to evaluate the impact of the protocol on donors who completed it successfully.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The participant-level (donor) dataset will be made available to all study investigators and their respective OPOs. It may be provided to other OPOs, on request. No recipient outcome data will be shared.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center is comprised of the study PIs and the central study statistician. The coordinating center will be responsible for oversight of the study. The study statistician will review data entered by study sites for completeness and perform periodic checks for accuracy. The central study coordinator will ensure transfer of additional donor-related data and demographics for each enrolled donor to the central database on a quarterly basis. The respective study OPOs will provide donor data only and not be involved in collecting or analyzing recipient data.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data and safety monitoring committee (DSMC) will be composed of several experienced but independent transplant researchers covering a wide range of expertise.

DSMC Member	Expertise	Institutional Affiliation
Krista Lentine, MD, PhD **CHAIR**	Transplant Physician and Researcher SRTR senior scientist	Professor of Medicine with tenure, Co-director of Clinical Research, Medical Director of Living Donation, SSM Health Saint Louis University Transplant Center
Farhan Zafar, MBBS	Thoracic Transplant Surgeon (Pediatrics)	Assistant Professor, Department of Surgery, University of Cincinnati
Mark Schnitzler, PhD	Transplant Researcher and Statistician SRTR senior scientist	Professor of Surgery with tenure, Director of Clinical Research, SSM Health Saint Louis University Transplant Center
Michael Souter, MB,ChB, DA, FNCS	Medical director of organ procurement organization	Professor and Chief of Anesthesiology, Harborview Medical Center, University of Washington Medicine Medical Director, LifeCenter Northwest OPO
Jason Eberl, PhD	Medical Ethicist	Professor and Director, Albert Gnaegi Center for Health Care Ethics, Saint Louis University
Jon Snyder, PhD, MS	Transplant Epidemiology and Statistical Analysis	Director, Scientific Registry of Transplant Recipients Director, Transplant Epidemiology, Hennepin Healthcare Research Institute

The DSMC statistician (Mark Schnitzler) will analyze the primary outcome and primary safety data at the time of the interim analysis. These results will be shared with the entire DSMC, who will discuss and provide a recommendation on whether to continue recruitment or whether to terminate the study. The DSMC members are independent from the study investigators and are not involved in the procedures of the study in other than this review and the review of any serious safety events.

Adverse event reporting and harms {22}

Study data forms include prospective ascertainment of adverse events entered by the organ procurement coordinators caring for each donor (events listed under *Outcomes, Safety Endpoints* and shown on forms provided in Appendix A). Any events deemed either related or potentially related to the study drug infusion will be reviewed the site coordinator. The site coordinator will report all AEs that are unanticipated and/or serious to the central site, within 72 hours, for further review. This includes all cases of cardiac arrest or donor instability leading to loss of the donor prior to organ recovery. These events, with narrative review, will be forwarded to the DSMB for review within one week. Incidence of all AEs (by study group) will be provided to the DSMB monthly and also be analyzed as part of the interim safety analysis. In addition, outcomes in the recipients receiving hearts from study participants will be analyzed in the interim analysis to ensure non-inferior graft function and survival.

Frequency and plans for auditing trial conduct {23}

The study statistician (in consultation with the study coordinator and study PI) will audit data and conduct of the trial and oversee and feedback given to each site coordinator.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Any important amendments to the protocol will be communicated to each study site within one week of the change. These will also be updated on clinicaltrials.gov.

Dissemination plans {31a}

The final study results will be presented internally at the meeting of investigators (part of the Organ Donation Research Council at AOPO) and communicated to the OPO community using the AOPO-plus (restricted) web portal. Findings will be presented in abstract form with plans for simultaneous publication at a major transplantation meeting.

Discussion

This trial was discussed with at the AOPO councils: of medical directors and of the Organ Donation Research Council. Feedback from these groups was incorporated into the study protocol. All OPOs were invited to participate and sent a survey to gauge interest.

Trial status

Recruitment began on : 01 December, 2020
Anticipated date of study completion: 31 December, 2022

Acknowledgements

We would like to acknowledge all the organ procurement coordinators who will perform the essential functions of this study and for caring for each of the donors involved in the study. We would also like to acknowledge each of the site coordinator for the study who collected all the data and ensured adherence to the study protocols and procedures.

Authors' contributions {31b}

All site investigators who participate in the study planning, conduct, and review study results and analyses are eligible to be authors on manuscripts resulting from the study. No outside professional writers or consultants will be utilized. The study statistician and central coordinator will also be included as authors. All these meet the criteria for authorship laid out by the International Committee of Medical Journal Editors. Any other people meeting those criteria will also be invited as co-authors. All authors will read and approve the final manuscript(s).

Funding {4}

No specific funding or financial support is provided to the PIs for performance of this study. However, administrative support will be provided by the study sponsor for effort to coordinate the study and perform statistical analyses. The sponsor will not have access to the primary study data or be involved in its analysis or interpretation. The sponsor will also not be involved in the writing of the manuscript.

Availability of data and materials {29}

The principal investigator will have final ownership over the dataset for this study. Data will be made available to any OPOs participating in the study and to other OPOs upon reasonable request.

Ethics approval and consent to participate {24}

This trial will not study or collect identifiable data on any human subjects. All donors enrolled in this study have been declared dead by neurologic criteria. However, this donor management study will be approved by the research/ethics committees at each participating OPO site. The study first received determination of non-human subjects status from the *Human Research Protection Office* at Washington University in St. Louis (the academic affiliation of the PI). The individual OPOs will not be collecting data on recipients and so will not be engaged in human subjects' research. The central study coordinators will use the UNOS IDs to obtain recipient outcome data through UNOS/SRTR. In order to collect recipient outcome data, we have submitted this study for additional IRB approval, to obtain waiver of recipient consent. The collection of de-identified recipient outcomes, as outlined, does not pose more than minimal risk to their privacy. The study will not influence how hearts are allocated to particular recipients or means of allocation. The study intervention (T4, a standard practice in donor management) will be disclosed as part of the DonorNet platform that transplant centers/surgeons review.

Consent for publication {32}

Not applicable

Competing interests {28}

RD is a consultant for Mid-America Transplant.
GM is an employee of Mid-America Transplant.

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References

1. Szabó G. Physiologic changes after brain death. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2004;23:S223-6.
2. Dujardin KS, McCully RB, Wijdicks EF, Tazelaar HD, Seward JB, McGregor CG, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. J Heart Lung Transplant. 2001;20(3):350-7.
3. Tryon D, Hasaniya NW, Jabo B, Razzouk AJ, Bailey LL, Rabkin DG. Effect of left ventricular dysfunction on utilization of donor hearts. J Heart Lung Transplant. 2018;37(3):349-57.
4. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. Transplantation. 1989;47(5):828-34.
5. Novitzky D, Cooper DK. Thyroid hormone and the stunned myocardium. J Endocrinol. 2014;223(1):R1-8.
6. Novitzky D, Cooper DKC, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: experimental and clinical studies. Transplantation. 2006;82:1396-401.
7. Novitzky D, Mi Z, Sun Q, Collins JF, Cooper DK. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. Transplantation. 2014;98(10):1119-27.
8. Cooper LB, Milano CA, Williams M, Swafford W, Croezen D, Van Bakel AB, et al. Thyroid hormone use during cardiac transplant organ procurement. Clin Transplant. 2016;30(12):1578-83.
9. Rosendale JD, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER, et al. Hormonal resuscitation yields more transplanted hearts, with improved early function. Transplantation. 2003;75:1336-41.
10. Macdonald PS, Aneman A, Bhonagiri D, Jones D, O'Callaghan G, Silvester W, et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. Critical care medicine. 2012;40:1635-44.
11. Goarin JP, Cohen S, Riou B, Jacquens Y, Guesde R, Le Bret F, et al. The effects of triiodothyronine on hemodynamic status and cardiac function in potential heart donors. Anesth Analg. 1996;83(1):41-7.
12. Dhar R, Stahlschmidt E, Yan Y, Marklin G. A randomized trial comparing triiodothyronine (T3) with thyroxine (T4) for hemodynamically unstable brain-dead organ donors. Clin Transplant. 2019:e13486.
13. Cooper DK, Novitzky D, Wicomb WN, Basker M, Rosendale JD, Myron Kauffman H. A review of studies relating to thyroid hormone therapy in brain-dead organ donors. Front Biosci (Landmark Ed). 2009;14:3750-70.
14. Dhar R, Stahlschmidt E, Marklin G. A Randomized Trial of Intravenous Thyroxine for Brain-Dead Organ Donors With Impaired Cardiac Function. Prog Transplant. 2020;30(1):48-55.
15. Sally M, Malinoski D. Current research on organ donor management. Anesthesiology clinics. 2013;31:737-48.
16. Minambres E, Perez-Villares JM, Chico-Fernandez M, Zabalegui A, Duenas-Jurado JM, Misis M, et al. Lung donor treatment protocol in brain dead-donors: A multicenter study. J Heart Lung Transplant. 2015;34(6):773-80.
17. Angel LF, Levine DJ, Restrepo MI, Johnson S, Sako E, Carpenter A, et al. Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. Am J Respir Crit Care Med. 2006;174(6):710-6.

18. Dhar R, Stahlschmidt E, Paramesh A, Marklin G. A Randomized Controlled Trial of Naloxone for Optimization of Hypoxemia in Lung Donors After Brain Death. Transplantation. 2019;103(7):1433-8.
19. Niemann CU, Feiner J, Swain S, Bunting S, Friedman M, Crutchfield M, et al. Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function. N Engl J Med. 2015;373(5):405-14.
20. Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, et al. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. JAMA. 2009;302:1067-75.
21. Ware LB, Landeck M, Koyama T, Zhao Z, Singer J, Kern R, et al. A Randomized Trial of the Effects of Nebulized Albuterol on Pulmonary Edema in Brain-Dead Organ Donors. American Journal of Transplantation. 2014;14:621-8.
22. Kotloff RM, Blosser S, Fulda GJ, Malinoski D, Ahya VN, Angel L, et al. Management of the Potential Organ Donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. Crit Care Med. 2015;43(6):1291-325.
23. Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet. 2015;385(9987):2577-84.
24. Zuppa AF, Nadkarni V, Davis L, Adamson PC, Helfaer MA, Elliott MR, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. Crit Care Med. 2004;32(11):2318-22.